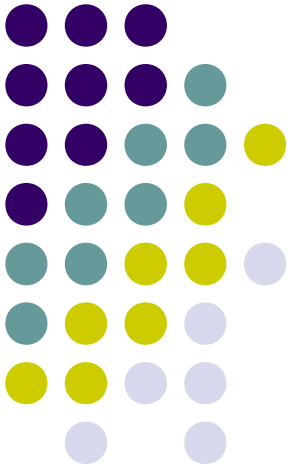
FDA Perspective on Nanomaterial-Containing Products

Nakissa Sadrieh, Ph.D.
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Nanobusiness Conference, May 2005



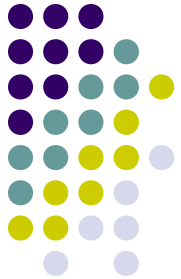
FDA Mission

- The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for **advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable**; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

FDA Organization

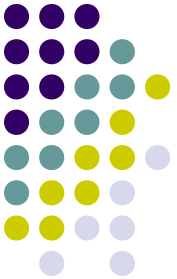
- Agency within the Department of Health and Human Services.
- Consists of 8 Centers/Offices:
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)
  - Center for Drug Evaluation and Research (CDER)
  - Center for Food Safety and Applied Nutrition (CFSAN)
  - Center for Veterinary Medicine (CVM)
  - National Center for Toxicological Research (NCTR)
  - Office of the Commissioner (OC)
  - Office of Regulatory Affairs (ORA)

FDA REGULATED PRODUCTS



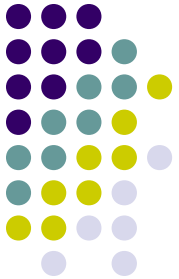
- Foods
  - All interstate domestic and imported, including produce, fish, shellfish, shell eggs, milk (not meat or poultry)
  - Bottled water
  - Wine (<7 alcohol)
  - Infant formula
- Food additives
  - Colors
  - Food containers
- Cosmetics
- Dietary Supplements
- Animal Feeds
- Pharmaceuticals
  - Human
  - Animal
  - Tamper resistant packaging
- Medical devices
- Radiation emitting electronic products
- Vaccines
- Blood products
- Tissues
- Sterilants
- Counter-terrorism products

FDA Regulates Products on a Product-by-Product Basis



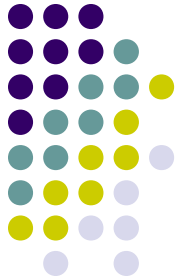
- **Pre-market approval**
  - For products that require an FDA approval prior to introduction to the market.
- **Market clearance**
  - For products that are similar to products that were cleared to market previously, or are prepared to approved specifications. FDA review process for these products is more rapid than for pre-market approval.
- **Post-market review**
  - For these products, market entry and distribution are at the discretion of the manufacturer and FDA monitors the behavior of these products. Regulatory action is taken if adverse events occur.

Current Trends in Drug Discovery



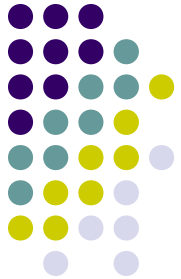
- At a time when basic biomedical knowledge is increasing, the gap between bench discovery and bedside application appears to be expanding.
- Current medical product development path is increasingly challenging, inefficient and costly.
- There is a crisis in moving basic discoveries to the market and ultimately to patients.
- Recent analysis of the pipeline problem was conducted by FDA and resulted in the publication of the Critical Path Initiative (March 2004) (http://www.fda.gov/initiatives/criticalpath/)

FDA's Critical Path Initiative



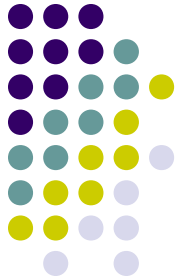
- Initiative to help reduce existing hurdles in medical product design and development.
- Initiative rooted in taking advantage of innovative science and technologies to reach commercialization of medical products.
- 3 crucial scientific/technical dimensions on the critical path from scientific discovery to commercial product have been identified: assessing safety, demonstrating medical utility and industrialization.
- **Nanotechnology is an element under evaluation in FDA's Critical Path Initiative.**

FDA Activities in Nanotechnology



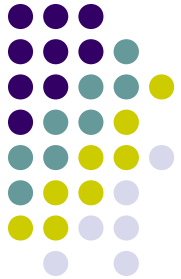
- Office of Science and Health Coordination (within OC) coordinates regular discussions within Agency.
- Individual Centers have regular discussion groups within each Center.
  - Purpose of these meetings is to insure awareness of policies that may be developing within the Agency and to educate staff and policy makers on scientific progress in nanotechnology.
- Interagency Oncology Task Force, Nanotechnology subcommittee, featuring collaboration between FDA-NCI-NIST

Coordination of Policy on Nanomaterials with Other Agencies



- FDA is a member of the Nanoscale Science and Engineering Technology (NSET) Subcommittee of the National Science and Technology Council (NSTC) Committee on Technology.
- FDA co-chairs with NIOSH the NSET Working Group on Nanomaterials Environmental and Health Implications (NEHI) to define new test methods to assess safety of these products.
- FDA contributes to the evaluation of the toxicity of materials supported by NIEHS and NTP.

Current FDA Definition of Nanotechnology

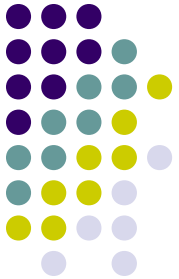


- FDA calls it "nanotechnology" only if it involves all of the following:
  - 1. Research and technology development, or products regulated by FDA, that are at the atomic, molecular or macromolecular levels, and where at least one dimension, that affects the functional behavior of the product, is in the length scale range of approximately 1-100 nanometers.
  - 2. Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
  - 3. Ability to control or manipulate at the atomic scale.

Historically

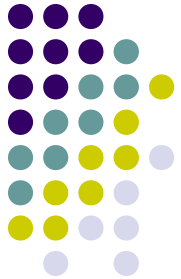
- FDA has approved many products with particulate materials in the nanosize range.
- Most drugs are expected to go through a nanosize phase during the process of absorption in the body.
- There have been no safety concerns reported in the past because of particle size.

Applications of Nanoparticles to Drug Discovery and Biology



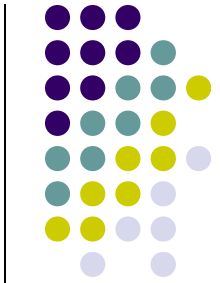
- Fluorescent biological markers
- Detection of proteins
- Probing of DNA structures
- Separation and purification of biological molecules and cells
- MRI contrast enhancement
- Tumor destruction via heating
- Tissue engineering
- Drug and gene delivery (Nanomarkets, March 2005)

Trends in Development of Nanoparticles in Medicine



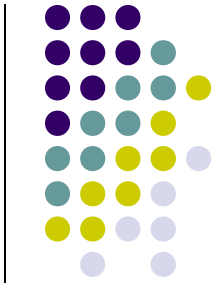
- Currently, nanoparticle applications in medicine are geared towards drug discovery and drug delivery (Quantum Dots, gold nanoparticles, Nanoshells for Raman spectroscopy, Nanobarcode particles).
- In the future, the goal is to make the nanoparticles multifunctional and controllable by external signals or local environments (nano-devices?) (Nanomarkets, March 2005)

Possible Opportunities for Nanotechnology in Drug Delivery



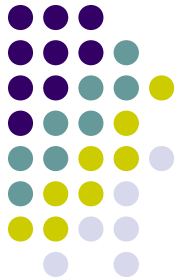
- Enhanced drug properties such as:
  - Solubility
  - Rate of dissolution
  - Oral bioavailability
  - Targeting ability
- Enhanced dosing requirements:
  - Lower dosed administered
  - Better side effect profile
  - More convenient dosage forms

FDA-Regulated Products Expected to be Impacted by Nanotechnology



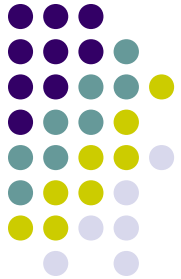
- Drugs (novel NMEs or delivery systems)
- Medical devices
- Biotechnology products
- Tissue engineering products
- Vaccines
- Cosmetics
- Combination products

What are Combination Products?



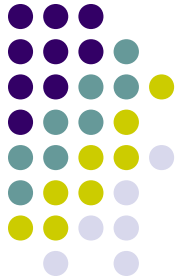
- Combination products are made of multiple constituents: drug-device, drug-biologic, device-biologic or drug-device-biologic that are physically or chemically combined, co-packaged in a kit or separate cross-labeled products.
- All components work as a system and are critical to achieve desired therapeutic effect.

Who Regulates Combination Products?



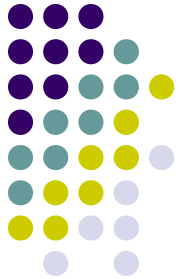
- Office of Combination Products (established in 2002 under Medical Device User Fee and Modernization Act).
- Jurisdiction for regulatory responsibility assigned to a lead Center, based on the "primary mode of action" (most important therapeutic action) of the combination product (proposed rule defining PMOA published in Federal Register on May 7th, 2004).
- www.FDA.gov/oc/combination

Examples of Nanotechnology Combination Product



- Multi-component system that may consist of:
  - Carrier/delivery system (drug or device)
  - Therapeutic agent (drug or biologic)
  - Imaging agent
  - Targeting agent
- Implantable microchip-based delivery systems that deliver different drugs under controlled conditions.
- Injectable delivery systems (transdermal microneedles). (Nanomarkets, March 2005)

General Concerns about Nanotechnology Products

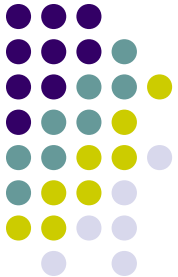


- Examples of concerns regarding:
  - Safety
  - Quality of material/characterization
  - Environmental

Safety Concerns

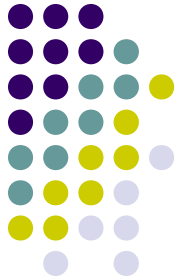
- As particle size gets smaller, there may be size-specific effects on activity, such as:
  - Will nanoparticles gain access to tissues and cells that normally would be bypassed by larger particles?
  - Once nanoparticles enter tissues, how long do they remain there and how are they cleared?
  - If nanoparticles enter cells, what effects do they have on cellular and tissue functions? Might there be different effects in different cells types?

Safety Concerns (Cont'd)



- What are the differences in the ADME profile of nanoparticles versus larger particles?
- What preclinical screening tests would be useful to identify potential risks (in vitro or in vivo)?
- Can new technologies such as "omics" help identify potential toxicities and how can these methodologies complement current testing requirements?
- Can nanoparticles gain access to the systemic circulation from dermal exposure? If nanoparticles enter skin cells, is there an effect on cellular functions? This would be relevant to drugs and cosmetics.

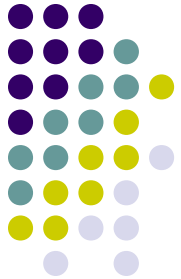
Characterization Concerns



- What are the forms in which particles are presented to host, cells and organelles?
- What are the critical physical and chemical properties, including residual solvents, processing variables, impurities and excipients?
- What are the standard tools used for this characterization?

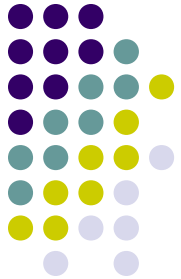
- What are validated assays to detect and quantify nanoparticles in tissues, medical products, foods and processing equipment?
- How do physical characteristics impact product quality and performance?
- How do we determine long and short-term stability of nanomaterials?

Environmental Concerns



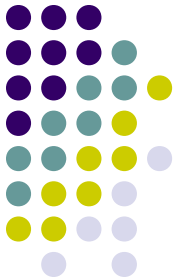
- Can nanoparticles be released into the environment following human and animal use?
- What methodologies would identify the nature, and quantify the extent, of nanoparticle release in the environment?
- What might be the environmental impact on other species (animals, fish, plants, microorganisms)?

Current Preclinical Tests for Safety Evaluation



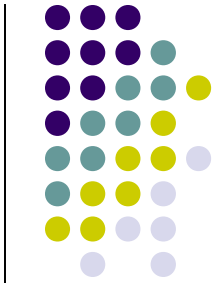
- Pharmacology
- Safety pharmacology
- Toxicology (including clinical pathology and histopathologic analysis)
- ADME
- Genotoxicity
- Developmental toxicity
- Immunotoxicity
- Carcinogenicity
- Other

Adequacy of Current Preclinical System?



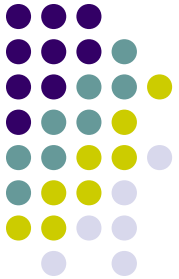
- Existing battery of preclinical tests is currently believed to be adequate.
- Why?
  - High dose multiples used
  - At least 2 animal species used
  - Extensive histopathology on most organs
  - Functional tests (cardiac, neurologic, respiratory, reproductive, immune system, etc/ ...)
  - Extended treatment periods (up to 2 years for carcinogenicity studies)

FDA Research in Nanotechnology



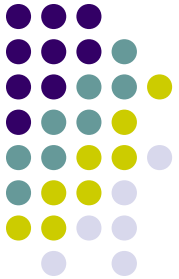
- Examples of research in
  - CDER
  - CBER
  - NCTR
  - CFSAN

Examples of CDER Research in Nanotechnolgy



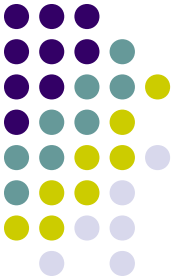
- Particle size determination in marketed sunscreens with TiO_2 and ZnO nanoparticles.
- Development of in vitro assays to assess toxicity of selected nanoparticles (collaboration with CDRH).
- Manufacture of nanoformulations and characterization of physical and chemical properties.

Examples of CDER Research in Nanotechnolgy (Cont'd)



- Evaluation of excipient effects on nanotechnology products.
- Evaluation of the effects of preparation methodology, process and formulation variables on nanotechnology product characteristics (including mathematical modeling of variables).
- Evaluate the stability and pre-clinical bioavailability of certain selected nanotechnology products.

Examples of CBER Research in Nanotechnolgy



- Development of Nanoparticle-Based Bio-Bar Code Amplification Multiplex Assays for Detection of Blood Born Viruses.

- Development of Assays for Testing of Vascular and Blood Cell Compatibility of Nanomaterials.

Examples of CFSAN Research in Nanotechnogy in Cosmetics

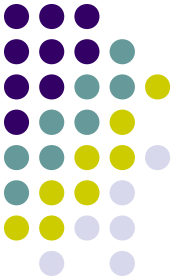
Collaboration with NCTR/NTP/Rice U.:

- Evaluating the effects of varying nano-size on the penetration of quantum dots through human and pig skin.
- Evaluating the penetration of TiO_2 and ZnO nanoparticles through human skin.
- Evaluating the photocytotoxicity of TiO_2 nanoparticles using human skin fibroblasts.

Examples of NCTR Research in Nanotechnology

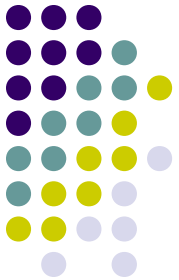
- Evaluating the effect of size and coating on dermal penetration of quantum dots in skin of hairless mice (collaboration with NTP and Rice University)
- Evaluating the toxicology of nanoscale TiO_2 and ZnO: market survey (size and coating); dermal penetration in vitro & in mice and pigs; PK and toxicogenomics in mice; phototoxicity in vitro & mice; photocarcinogenicity in mice (collaboration with NTP, CFSAN and Rice University)

Two Frequently Asked Questions



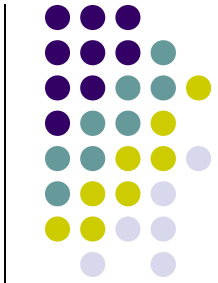
- Who (which Center) will review nanotechnology products?
- What will be the requirements for nanotechnology products?

Who Will Review Nanotechnology Products?



- Office of Combination Products will coordinate the regulatory framework for nanotechnology products.
- An FDA Center will be designated with the primary responsibility for review.
- However, consultations from other Centers will be sought.

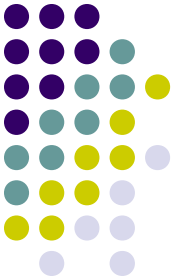
What Are Testing Requirements for Nanotechnology Products?



- Currently there are no testing requirements that are specific to nanotechnology products.

- FDA's current requirements for safety testing of products is very rigorous. However if research identifies toxicological risks that are unique to nanomaterials, additional testing requirements may become necessary.

Nanotechnology Product-Specific Guidance Document?

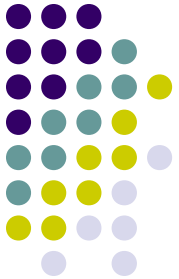


- FDA is not anticipating any new guidance documents regarding nanomaterials in the near future.
- The process of approval for nanomaterials will be the same as that used for other products making the same claims.

Challenges

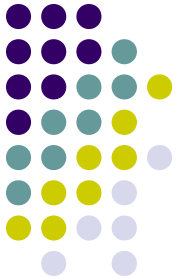
- New technology: unknown risks
- Limited scientific data available to address public health concerns.
- Timely and accurate reporting of all relevant scientific findings.
- Working in multidisciplinary teams.
- Nomenclature
- Pharmaceutical equivalence and bioequivalence (generic drugs).

Crucial Hurdles for Nanotechnology



- **Safety assessment**
  - Adequacy of current toxicologic screens for nanoscale materials.
  - Potential for novel, unanticipated reactions.
  - Environmental consequences of medical use.
- **Medical utility**
  - No experience with clinical testing.
- **Industrialization**
  - Understanding the physical and chemical parameters that are crucial to product performance.
  - Developing test methods and specifications to control product/process.
  - Scale-up to mass production.
  - Lack of reference material, standards and manufacturing standardization.

Standard Test Method for Biological Response Including Particles

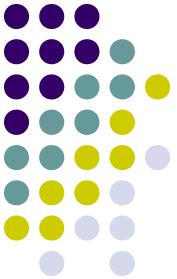


- Guidelines for evaluating biological safety for medical devices is based on application of voluntary standards
  - ASTM F 748 (F1903 in vitro and F1904 in vivo, for particles)
  - ISO 10993, Part 1
- None of the standards are specific for nanoparticles.
- Additional standard test methods may need to be developed for nanoparticles.
- No existing standards for testing particles for drugs and biologics.

Opportunities

- Early involvement of all parties: crucial for conducting appropriate research and for identifying useful applications and potential risks.
- Open communication between developers of nanotechnology products and regulators.
- Education: risk communication

FDA Nanotechnology Website



- For links to individual Centers, published guidance documents and other relevant information on nanotechnology activities at FDA:

  - **www.FDA.GOV/NANOTECHNOLOGY**
  - **Sadriehn@CDER.FDA.GOV**